Research

Research Project: Characterization and Control of Nutritional and Sensory Properties of Raw and Processed Grains, Legumes and Vegetables

Location: Processed Foods Research

Title: Identification of **Benzalkonium** Chloride in Commercial Grapefruit Seed Extracts

Authors
- Takeoka, Gary
- Dao, Lan
- Wong, Rosalind - *roz*
- Harden, Leslie - *les*

Submitted to: Journal of Agricultural and Food Chemistry
Publication Type: Peer Reviewed Journal
Publication Acceptance Date: August 1, 2005
Publication Date: August 12, 2005
Citation: Takeoka, G.R., Dao, L.T., Wong, R.Y., Harden, L.A. 2005. Identification of **Benzalkonium** Chloride in Commercial Grapefruit Seed Extracts. Journal of Agricultural and Food Chemistry. 53:7630-7636.

Interpretive Summary: Grapefruit seed extract (GSE) is promoted as a natural product that has reported antibacterial and antiviral properties. It is reported to be safe and effective to use internally and externally for a wide variety of conditions such as acne, allergies,

Project Team
- Takeoka, Gary
- Wong, Rosalind - *Roz*
- Berrios, Jose
- McHugh, Tara

Publications
- Publications

Related National Programs
- Quality and Utilization of Agricultural Products (306)

Related Projects
- Concentration of Proteins from Legumes on a Pilot Plant Scale

athlete¿s foot, body odor, candida, colds, cold sores, gastrointestinal infections, gingivitis, impetigo, parasitic infection, sinusitis, sore throat and thrush. There is recent evidence that some commercial GSE samples are adulterated with synthetic preservatives and that these additives are solely responsible for the antimicrobial activity. Preservatives such as methyl 4-hydroxybezoate (methyl paraben), 2,4,4¿-trichloro-2¿-hydroxydiphenyl ether (triclosan) and **benzethonium** chloride have been identified in commercial GSE samples. In this study we identified a new synthetic adulterant, **benzalkonium** chloride, in commercial GSE samples. This ingredient is a synthetic antimicrobial agent that is widely used in cleaning and disinfection agents. The presence of **benzalkonium** chloride in a commercial product designated for internal and external use by humans is troubling in light of its **toxicity** and allergenicity.

Technical Abstract: Commercial grapefruit seed extracts (GSE) were extracted with chloroform. The solvent was evaporated, and the resulting solid was subsequently analyzed by high performance liquid chromatography, electrospray ionization mass spectrometry (ESI/MS) and tandem mass spectrometry (ESI/MS/MS), and elemental analysis (by proton induced X-ray emission [PIXE] analysis). Three major constituents were observed by HPLC and were identified as benzyldimethyldodecylammonium chloride, benzyldimethyltetradecylammonium chloride, and benzyldimethylhexadecylammonium chloride. This mixture of homologues is commonly known as **benzalkonium** chloride, a widely used synthetic antimicrobial ingredient used in cleaning and disinfection agents.

Last Modified: 07/29/2006

Proc. West. Pharmacol. Soc. **44:** 197-199 (2001)

Intrathecal Ketamine in Surgeries for Lower Abdomen and Lower Extremities

KALIYANI GOVINDAN, RAJMANI KRISHNAN, MARC P. KAUFMAN, RAFIK MICHAEL, RICHARD J. FOGLER & JONAS GINTAUTAS*

The Brookdale University Hospital And Medical Center, 1 Brookdale Plaza, New York, NY, USA 11212

Ketamine is a phencyclidine derivative with potent analgesic properties that gained popularity as sole iv anesthetic for short surgical procedures. Its modes of action and uses have been reviewed and include both antagonism at NMDA receptor and a local anesthetic effect [1]. Ketamine produces a functional dissociation between the thalamocortical and limbic systems, a state that has been termed "dissociative anesthesia" [2]. It depresses the neuronal function in the cerebral cortex and thalamus, while simultaneously activating the limbic system. Its effect on the medial medullary reticular formation may be involved in the affective component of its nociceptive activity [3].

There is evidence from animal studies that **ketamine** produces sensory [4,5] and motor [5,6] blocks when injected intrathecally. **Preservative**-free **ketamine** hydrochloride was introduced as a spinal anesthetic more than twenty years ago and found to have advantages over local anesthetics in that it did not produce hypotension. It was used in humans as a sole spinal anesthetic agent by Bion [7] in patients undergoing surgeries for lower limb injuries. We have assessed the efficacy of **ketamine** as a sole spinal anesthetic agent for elective surgeries of the abdomen and lower limbs, to compare the different dosage schedules of **ketamine** on the duration of analgesia and to evaluate the efficacy of adding epinephrine to **ketamine** on the quality and duration of analgesia.

METHODS: A double blind randomly controlled study was done on

eral decubitus position using a 22 G Whitacre needle via the L 2-3 3-4 intervertebral spaces. The subarachnoid placement of the need was confirmed by free aspiration of CSF and then a predetermine dose of the drug was injected as per the group allocation. The pati was then placed supine and the effect of the anesthetic was observ The level of analgesia, motor blockade, central effects, and evalua of cardiovascular stability was recorded.

Sensory block was assessed by response to pin prick with a 2 sharp needle. A modified Bromage score tested motor block: 0 – 1 motor loss, 1-inability to flex the hip, 2-inability to flex the knee, inability to flex the ankle.

Central effects were assessed by the level of sedation: 0- fully scious, 1- drowsiness, 2-asleep but arousable, 3-unarousable with of verbal contact.

Evaluation of cardiovascular stability was done by recording heart rate, blood pressure and respiratory rate immediately before after the injection, followed by every 2 min for the first 15 min an every 5 min thereafter throughout the surgery and until the compl reversal of analgesia and motor blockade.

Any complications like nausea, vomiting, nystagmus or deliri that occurred in the intraoperative and postoperative periods were recorded.

The observations were analyzed using the Student`s t test to c pare the data between the groups. P value < 0.05 was taken as stat cally significant.

RESULTS: It was observed that increasing the dosa **ketamine** from 75 to 100 mg did not significantly al onset of sensory and motor blocks but that there was nificant increase in the duration of the blocks (Table In both the dosages, motor blockade was longer than sory blockade. A higher dosage produced a higher l

60 patients scheduled for surgeries, to evaluate the efficacy of intrathecal **preservative**-free **ketamine** in various dosages (75 mg, 100 mg in 5% dextrose), with and without 1:200,000 epinephrine, controlling the specific gravity of the solutions. Patients had no history of neurologic or psychiatric illness and had no contraindication to regional anesthesia. An informed written consent for the anesthetic was obtained. The Institutional Review Board approved the study. The patients were divided into 4 groups of 15 each using computer generated random numbers. The first group (A1) of patients received 75 mg **ketamine**; the second group (A2) 75 mg **ketamine** with epinephrine, the third group (B1) 100 mg **ketamine** and the fourth group (B2) received 100 mg **ketamine** with epinephrine. **Preservative**-free **ketamine** hydrochloride, 50 mg/ml, was used for producing spinal analgesia. As it was found to be hypobaric, 5% dextrose was added to make it hyperbaric. The total volume injected was 3 ml in all patients.

The patients received no premedication. In the operating room iv cannulation, noninvasive blood pressure monitoring and continuos electrocardiography was commenced. Equipment and drugs necessary for general anesthesia administration and resuscitation were kept ready. Spinal anesthesia was performed with patients in the right lat-

of analgesia. Addition of epinephrine to **ketamine** i the dosage schedules prolonged the duration of mot sensory blockades significantly. Level of analgesia not influenced by the addition of epinephrine (Table

It was observed that intrathecally-administered k mine caused a mild increase in pulse rate and systol pressure in all four groups (Table 2A). The rise was dose-dependent and the addition of epinephrine did have any significant effect on the parameters (Table Vomiting was noted in two patients and delirium in patient, which was treated with diazepam (0.1 mg/k Post spinal headache was noticed in 12% of the pati

DISCUSSION: Intrathecal **ketamine** has been stud extensively in animals, but rarely used in humans. It known to produce both motor and sensory block, bu

Table 1. Effect of different dosages of **ketamine** alone (A) and with epinephrine (B) on onset, duration, and peak levels of sensory (analgesia) and motor (paralysis) blocks

A. Outcome measurement	Ketamine 75 mg	Ketamine 100 mg	*p* value
Onset of analgesia (min)	1.23 ± 0.31	1.22 ± 0.51	0.945
Duration of analgesia (min)	42.3 ± 3.8	78.3 ± 10.0	0.000*
Onset of paralysis (min)	1.98 ± 0.54	2.18 ± 0.73	0.435
Duration of paralysis (min)	53.6 ± 8.6	87.00 ± 7.27	0.000*
Peak level of analges ia(mean	T8.7 ± 1.2	T6.2 ± 0.9	_

B. Outcome measurement	Ketamine 75 mg	Ketamine 75 mg + epinephrine	*p* value	Ketamine 100 mg	Ketamine 100 mg + epinephrine
Onset of analgesia(min)	1.23 ± 0.31	1.08 ± 0.34	0.232	1.22 ± 0.51	1.08 ± 0.13
Duration of analgesia(min)	42.33 ± 3.84	75.4 ± 9.77	0.000*	78.26 ± 10.18	97.66 ± 12.37
Onset of paralysis(min)	1.98 ± 0.54	2.21 ± 0.62	0.283	2.18 ± 0.73	2.2 ± 0.52
Duration of paralysis(min)	53.66 ± 8.56	91.46 ± 11.9	0.000*	87.00 ± 7.27	106.66 ± 8.99
Peak level of analgesia(mean	T8.7 ± 1.24	T8.4 ± 1.06	_	T6.2 ± 0.88	T6.6 ± 1.11

All values are ± SD. * *p* value of < 0.05 is taken as statistically significant.

Table 2. Effect of increase in dosage of **ketamine** alone (A) and with epinephrine (B) on pulse rate and blood pressure

A. Outcome measurement	Ketamine 75 mg	Ketamine 100 mg	*p* value

Pulse rate			
Control	78 ± 6	81.9 ± 5.6	
Maximum	85.2 ± 5.5	88.5 ± 5.3	0.136
Systolic BP			
Control	123.4 ± 6.4	125.02 ± 6.2	
Maximum	128.26 ± 7.7	131.06 ± 7.12	0.140

B. Outcome measurement	Ketamine 75 mg	Ketamine 75 mg + epinephrine	*p* value	Ketamine 100 mg	Ketamine 100 mg + epinephrine
Pulse rate					
Control	78.6 ± 5.7	78.9 ± 6.2		81.86±5.6	84.9 ± 4.9
Maximum	85.2 ± 5.5	86.5 ± 5.6	0.533	88.46±5.3	91.9 ± 3.7
Systolic BP					
Control	123.4 ± 6.4	124.6 ± 5.6		125.0 ± 6.2	125.2 ± 4.9
Maximum	128.3 ± 7.7	128.9 ± 7.1	0.807	131.1 ± 7.1	130.3 ± 5.8

All values are ± standard deviation. * p value of < 0.05 is taken as statistically significant.

mechanism of action is not clear [8]. **Ketamine** acts at NMDA, opiate, monoaminergic, muscarinic receptors [9-11] and voltage-sensitive calcium channel blockers and it is also thought to have some local anesthetic property [1,4].

Hawksworth *et al.* [8] studied intrathecal **ketamine** (0.75-0.9 mg/kg) in patients undergoing transurethral resection of the prostate. Of the 10 patients studied, six required general anesthesia because of inadequate surgical analgesia. The study was abandoned because of the high incidence of central effects. Sandler *et al.* [12] sugg that epidural **ketamine** may have an additive effect opioids and local anesthetics. Kathirvel *et al.* [13] st the effect of intrathecal **ketamine** added to bupivac and found that it had local anesthetic sparing effort, the high incidence of adverse effects limited its use.

Smith and Peko [14] and Finck and Ngai 10] rep that **ketamine** has agonist action at opiate receptors. lowing, this Bion [7] used **ketamine** to produce sur anesthesia, injecting it intrathecally for war injuries,

found no interference with cardiovascular or respiratory functions. Bion used 5-50 mg **ketamine**. The mean onset time of analgesia was 1.7 min and duration was 45-90 min. Our study also showed that that mean onset time of analgesia was 1.5-2 min and that the duration varied between 45-120 min, depending on the dosage used. Our observation that increase in dosage caused an increase in duration of analgesia was consistent with Bion's observations, but he had obtained results similar to us with lower dosage schedules. He concluded that satisfactory anesthesia was produced only with 50 mg or more of **ketamine**. He also reported that addition of epinephrine caused profound motor blockade, and concluded that epinephrine augmented the effect of **ketamine**, which was consistent with our finding. We found that 75 mg **ketamine** pro-

tion. With the use of hyperbaric solution of **ketamir** all our patients, we were able to obtain blockade up level with 75 mg and T6 level with 100 mg.

Regarding the side effects of **ketamine**, 86% of tients had nystagmus, 12% had post spinal headache had vomiting and one patient had delirium that need be treated with iv diazepam. Standard references qu the incidence of post spinal headache between 13-2(after the administration of intrathecal local anestheti The nystagmus and sedation noticed in most of our tients could either be due to the systemic absorption the drug or due to circulation of the drug via the CS the lateral ventricles. The cardiovascular stability wi slight increase in pulse rate and systolic blood press seen in our study are consistent with similar observa

duced motor paralysis in 73% of patients, while addition of epinephrine produced complete paralysis in all the patients. Bion attributes the action of epinephrine to analgesia rather than to delaying the spinal anesthesia by vasoconstriction. In his study, analgesia outlasted motor weakness, but in our patients motor blockade was longer than sensory blockade.

Our observations were also consistent with those of Bansal *et al.* [15] who had evaluated intrathecal **ketamine** for emergency surgeries of the lower limbs in 50 mg, 75 mg and 100 mg dosage schedules and epinephrine. With 75 mg, they were able to obtain sensory loss for 41 min and motor loss for 47 min. Our average values for the same dosage were 42.3 and 53.6 min, respectively. They also observed the increase in duration of sensory motor blockades by addition of epinephrine. With 100 mg of **ketamine**, the mean durations of sensory and motor blockades were 69.3 and 80 min, respectively. We obtained durations of 75.4 and 91.6, respectively. Thus, the duration was prolonged significantly by the addition of epinephrine in both dosage groups.

The addition of vasopressors to local anesthetics to prolong the duration of action has been studied by various researchers [16-18]. All have reported that intrathecally-administered epinephrine prolongs the duration of local anesthetics. Collins [16] concludes that spinally administered epinephrine may prolong the duration of local anesthetics via vasoconstriction or activation of antinociceptors or both.

The effect of baricity of the local anesthetic solution on the level of anesthesia has been studied by Lee *et al.* [19]. They concluded that hyperbaric local anesthetic solutions produce thoracic levels of anesthesia owing to the gravitation of the solution to the thoracic curvature. Banister and associates reported that glucose in hyperbaric solutions may delay the absorption of the drug by spinal cord [20]. Studies of plasma concentrations of hyperbaric local anesthetics after spinal administration have shown that absorption is faster with a glucose-containing solu-

of other investigators. The intensity of sedation in o patients was only mild or moderate with patients be easily arousable from the sleep.

In conclusion, intrathecal **ketamine** can be used cally in selected patients to produce adequate anesth for lower abdomen and lower extremities. Increasin dosage of **ketamine** and addition of epinephrine pro the duration of spinal anesthesia. Postoperative side like vomiting or delirium were noticed in a negligib centage of patients. Due to the cardiovascular stimu action of **ketamine**, there was a mild rise in heart ra blood pressure, which is a definite advantage over l anesthetics.

REFERENCES

1. Hirota K & Lambert DG: Br J Anesth 77: 441-444 (1996).
2. Winters WG, Ferrer-Allado T & Guzman-Flores C: Neuropharmacology 11: 303-315 (1972).
3. Reich DL & Silvay G: Can J Anaesth 36: 186-197 (1989).
4. Iida H, Dohi S, Tanahashi T, Watanabe Y & Takenaka M: Ane Analg 85: 106-110 (1997).
5. Dowdy EG, Kaya K & Gocho Y: Anesth Analg 52: 83-842 (19
6. Crisp T, Perrotti JM, Smith DL, Stafinsky JL & Smith DJ: Eur Pharmacol 194 167-172 (1991).
7. Bion J: Anesthesia 39: 1023-1028 (1984).
8. Hawksworth C & Serpell M: Reg Anesthesia 23: 283-288 (199
9. Irifune M, Shimizu T, Nomoto M & Fukuda T: Brain Res 596: (1992).
10. Finck AD & Ngai SH: Anesthesiology 1982: 56: 291-297 (19
11. Tung A & Yaksh T: Reg Anesthesia 6: 91-94 (1981).
12. Sandler AN, Schmid R & Katz J: Can J Anaesth 45: 99-102 (1998).
13. Kathirvel S, Sadasivam S, Saxena A, Kannan TR & Ganjoo P Anesthaesia 55: 899-910 (2000).
14. Smith DJ & Pekoe GM: Anesthesiology 53: 3-4 (1980).
15. Bansal SK & Bhatia VK: Indian J Anesth: 1: 32-42 (1994).
16. Collins JG Anesthesiology 60: 269-272 (1984).
17. Moore DC, Chadwick HS & Ready LB: Anesthesiology: 67: (1987).
18. Conception M: Anesth Analg 63: 134-138 (1984).
19. Lee A, Ray D, Littlewood D & Wildsmith: JA Br J Anaesth 6 (1988).
20. Bannister J, McClure JH & Wildsmith JA: Br J Anaesth 64:23 (1990).

OSHA Hazard Information Bulletins
Human Exposure and Adverse Drugs Reaction from Vetalor (**ketamine** hydrochloride).

OSHA Hazard Information Bulletins - Table of Contents by Year

- **Information Date:** 19890112
- **Record Type:** Hazard Information Bulletin
- **Subject:** Human Exposure and Adverse Drugs Reaction from Vetalor (**ketamine** hydrochloride).

January 12, 1989

MEMORANDUM FOR:	REGIONAL ADMINISTRATORS
THROUGH:	LEO CAREY Director Office of Field Programs
FROM:	EDWARD BAIER Director Directorate of Technical Support
SUBJECT:	Health **Hazard Information Bulletin**: Human Exposure and Adverse Drugs Reaction from Vetalor (**ketamine** hydrochloride) at Parke Davis of Morris Plains, New Jersey

The Food and Drug Administration has notified us of a reported human exposure and adverse drug reaction at Parke Davis, Morris Plains, New Jersey to Vetalor (**ketamine** hydrochloride) (see attachments). Approximately, 75mg of Vetalor was accidentally squirted in the eye of veterinary assistant and within a few minutes the individual became unconscious which lasted about 10 minutes. She was treated and fully recovered after two and one-half hours but was still lethargic. No warnings or precautions were on the label to address accidental human exposure.

Compliance Officers should be aware of the hazards and related worker exposure from accidents with drugs on workers in research laboratories and related operations.

Attachments

Dept of Health and Human Services | ADVERSE DRUG REACTION, | Form
Public Health Service | LACK OF EFFECTIVENESS,| approved
Food and Drug Admin.(HFV-210) | PRODUCT DEFECT REPORT | OMB #0910-0012
5600 Fisher Lane | (Forward to address at | use of this
| left) | form is
| Attach all | prohibited
| correspondence that | after April
| to this reaction.) | 30, 1988

Note: This report is required by law (21 CFR 510.3001). Failure to report can result in withdrawal of approval of the application.

1. REPORT SOURCE AND ADDRESS (mfr.distr.)|2. DATE SENT TO FDA |3. TYPE OF
Olga Woo | (Month, day, year) | REPORT
San Francisco Poison Control Center | 6-10-88 | X INITIAL
San Francisco, CA (US) | | follow up
| | to report
| | of (give
| | date)

4. NAME, ADDRESS AND PHONE # OF ATTENDING |5. NAME OR CASE
VETERINARIAN (In confidence) | IDENTIFICATION OF
| OWNER (In confidence
Gary Rich, MD |
Mills Hospital 100 S., San Mateo Drive | 88-5584-001
San Mateo, CA 94401 |
(415) 696-4500 |

SECTION I- DRUG DATA TOPICAL

6. TRADE, NAME AND GENERIC NAME(S) OF ACTIVE INGREDIENT(S)|7 a. Name of
(Include dosage form and strength. Ex. tab. 500 mg.) | Manufacturer
Vetalar (**ketamine** hydrochloride injection) | Parke Davis Co.
|b. NADA NO.
| 045-290 (164)AP

8. LOT NUMBER |9. DOSAGE REGIMEN AND ROUTE EX. 250 mg. |10. DATE(S) OF
| q 12 h.p.o.) | ADMINISTRATION
| | 02/03/88

11. ILLNESS/ REASON FOR USE OF THIS DRUG |12. DRUG WAS
| ADMINISTERED BY
|X VETERINARIAN,
| STAFF
| OWNER, OTHER

SECTION II- ANIMAL DATA

13. NUMBER OF ANIMALS IN THIS INCIDENT |14. REACTING ANIMAL(S)

a. TREATED WITH DRUG	b. REACTED	c. DIED	a. SPECIES	b. BREED
1	1	C	human	

15. CONCOMITANT MEDICAL PROBLEMS |c. AGE |d. WEIGHT
|e. SEX
| __female __pregnant
| __male __neutered

16. OVERALL STATE OF HEALTH AT TIME OF REACTION
__GOOD __ FAIR __ POOR X CRITICAL

17. DID ANY NEW ILLNESS DEVELOP OR DID INITIAL DIAGNOSIS CHANGE AFTER SUSPECT DRUG STARTED?
X NO __ YES (explain)

18. CONCOMITANT DRUGS ADMINISTERED

NAME OF DRUG	ROUTE	DOSAGE REGIMEN	DATE(S) OF ADMINISTRATION
0			

FOR FDA USE ONLY

1._____ __D __ NAI
2._____ __PR __ AI
3._____ __PO __ AP
4._____ __R __ AL
5._____ __NC
6._____
T._____
__ I.L. __ CL __ CONT

COMMENT
G- HUMAN EXPOSURE, EYE(S) -9 0 SE
N- UNCONSCIOUS -9 10 Mr
G- DEPRESSION/LETHARGY -9 2 HR
*VET ASSISTANT ACCIDENTALLY SQUIRTED IN EYE
*PERSON TAKEN TO EMERGENCY ROOM

FORM FDA 1932 (3/81)

SECTION III- REACTION DATA

19. DESCRIBE SUSPECTED ADVERSE REACTION: INCLUDE ALL SIGNS, RESULTS OF PERTINENT LAB TESTS, NECROPSY RESULTS. POSSIBLE CONTRIBUTING FACTORS, ETC. ALSO, INCLUDE IN THIS SECTION PRODUCT INEFFECTIVE AND PRODUCT DEFECTS SUCH AS CRACKED TABLETS, CLOUDY SOLUTION, ETC.

Unconsciousness in a veterinary assistant, due to inadvertent administration, in the eye of about 75 mg of Vetalar (**ketamine**). Within a few minutes of the accidental squirting, pt. remained unconscious for about 10 minutes when she was presented in ER, where, 2 1/2 hours later, had fully recovered but lethargic.

20. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT DRUG CAUSED REACTION
X HIGH ___MEDIUM ___LOW ___NO ATTENDING VET.

21. LENGTH OF TIME BETWEEN LAST ADMINISTRATION OF SUSPECT DRUG AND ONSET OF REACTION
Few minutes

22. DATE OF ONSET (mo., day. yr.)
02/03/88

23. DURATION OF REACTION (Hrs.,days)
10 Minutes

24. WAS THE ADVERSE REACTION TREATED?
X NO __ YES(Describe treatment

25. OUTCOME OF REACTION DATE
__ DIED (Give date)_____
__ REMAINS UNDER TREATMENT
__ ALIVE WITH SEQUELAE
X RECOVERED
__ UNKNOWN

26. WHEN REACTION APPEARED, TREATMENT SUSPECT DRUG:
X HAD ALREADY BEEN COMPLETED
__CONTINUED
__DISCONTINUED DUE TO THE REACTION
X STOPPED
__DISCONTINUED, REPLACED WITH ANOTHER DRUG
__DISCONTINUED, REINTRODUCED LATER

31. NAME AND TITLE OF INDIVIDUAL RESPONSIBLE FOR ACCURACY OF REPORTED INFORMATION (Type or print)
Jan L. Worster, MD Associate Director
Worldwide Adverse Event Reporting

Vetalar.
(**Ketamine** Hydrochloride Injection, USP)

Veterinary Injection For Intramuscular Use

DESCRIPTION Vetalar (**ketamine** hydrochloride) is a rapid-action, nonnarcotic, nonbarbiturate agent for anesthetic use in cats and for restraint in subhuman primates. It is chemically designated at 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride and is supplied as a slightly acid (pH 35 to 55) solution for intramuscular injection in a concentration containing the equivalent of 100 mg **ketamine** base per milliliter and contains not more than 01 mg/ml Phemerol (benzethonium chloride) as a **preservative**.

ACTION Vetalar is a rapid-action agent whose pharmacological action is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, mild cardiac stimulation and respiratory depression. Skeletal muscle tone is variable and may be normal, enhanced or diminished. The anesthetic state produced does not fit into the conventional classification of stages of anesthesia, but instead Vetalar produces a state of unconsciousness which has been termed "dissociative" anesthesia in that it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade. In contrast to other anesthetics, protective reflexes, such as coughing and swallowing are maintained under Vetalar anesthesia. The degree of muscle tone is dependent upon level of dose, therefore, variations in body temperature may occur. At low dosage levels there may be an increase in muscle tone and a concomitant slight increase in body temperature. However, at high dosage levels there is some diminution in muscle tone and a resultant decrease in body temperature, to the point where supplemental heat may be advisable. In cats, there is usually some transient cardiovascular stimulation, increased cardiac output with slight increase in mean systolic pressure with little or no change in total peripheral resistance. At higher doses respiratory rate is usually decreased. The assurance of a patent airway is greatly enhanced by virtue of maintained pharyngeal-laryngeal reflexes. Although some salivation is occasionally noted, the persistence of the swallowing reflex aids in minimizing the hazards associated with ptyalism. Salivation may be effectively controlled with atropine sulfate in dosages of 0.04 mg/kg (0.02 mg/lb) in cats and 0.01 to 0.05 mg/kg (0.005 to 0.025 mg/lb) in subhuman primates. Other reflexes, eg, corneal, pedal, etc., are maintained during Vetalar anesthesia, and should not be used as criteria for judging depth of anesthesia. The eyes normally remain open with the pupils dilated. It is suggested that a bland ophthalmic ointment be applied to the cornea if anesthesia is to be prolonged. Following administration of recommended doses, cats become ataxic in about 5 minutes with anesthesia usually lasting from 30 to 45 minutes at higher doses. At the lower doses, complete recovery usually occurs in 4 to 5 hours but with higher doses recovery time is more prolonged and may be as long as 24 hours. In studies involving 14 species of subhuman primates represented by a least 10 anesthesia episodes for each species, the median time to restraint ranged from 1.5 to 5.3 minutes [(Macaca nemestrina (pig-tailed macaque)] after injection. Recovery in generally smooth and uneventful. The duration is dose related. By single intramuscular injection. Vetalar usually has a wide margin of safety in cats and subhuman primates. In cats, cases of prolonged recovery and death have been reported.

INDICATIONS Vetalar may be used in cats for restraint or as the sole anesthetic agent for diagnostic or minor, brief, surgical procedures that do not require skeletal muscle relaxation. It may be used in subhuman primates for restraint.

CONTRAINDICATIONS Vetalar is contraindicated in cats and subhuman primates suffering from renal or hepatic insufficiency.

WARNINGS FOR USE IN CATS AND SUBHUMAN PRIMATES ONLY Vetalar is detoxified by the liver and excreted by the kidneys: therefore any pre-existent hepatic or renal pathology or impairment of function can be expected to result in prolonged anesthesia: related fatalities have been reported.

PRECAUTIONS In cats, doses in excess of 50 mg/kg during any single procedure should not be used. The maximum recommended dose in subhuman primates is 40 mg/kg. To reduce the

incidence of emergence reactions, animals should not be stimulated by sound or handling during the recovery period. However, this does not preclude the monitoring of vital signs.

ADVERSE REACTIONS Respiratory depression may occur following administration of high doses of Vetalar. If at any time respiration becomes excessively depressed and the animal becomes cyanotic, resuscitative measures should be instituted promptly. Adequate pulmonary ventilation using either oxygen or room air is recommended as a resuscitative measure. Adverse reactions reported have included amazes, salivation, vocalization, erratic recovery and prolonged recovery, spastic jerking movements, convulsions can be controlled by ultrashort-acting barbiturates which should be given to effect. The barbiturates should be administered intravenously at a dose level of one sixth of one fourth the usual dose fro the product being used. Acepromazine may also be used. However, recent information indicates that some phenothiazine derivatives may potentiate the toxic effects of organic phosphate compounds such as found in flea collars and certain anthelmintics. A study has indicated that **ketamine** hydrochloride alone does not potentiate the toxic effects of organic phosphate compounds.

DOSAGE AND ADMINISTRATION Vetalar is well tolerated by cats and subhuman primates when administered by intramuscular injection. Fasting prior to induction of anesthesia or restraint with Vetalar is essential: however when preparing for elective surgery, it is advisable to withhold food for a least six hours prior to administration of Vetalar. Anesthesia may be of shorter duration in immature cats. Restraint in subhuman primates neonates (less that 24 hours of age) is difficult to achieve.

Vetalar (**Ketamine** Hydrochloride Injection, USP) As with other anesthetic agents, the individual response to Vetalar is somewhat varied depending upon the dose, general condition, and age of the subject so that dosage recommendations cannot e absolutely fixed.

Dosage -- Cats: a dose of 11 mg/kg (4 mg/lb) is recommended to produce restraint. Dosages form 22 to 33 mg/kg (10 to 15 mg/lb) produce anesthesia that is suitable for diagnostic or minor surgical procedures that do not require skeletal muscle relaxation. Subhuman primates: The recommended restraints dosages of Vetalar for the following species are. Cercocebus torquatus (white-collared mangabey). Papio cynocephalus (yellow Baboon). Pan Troglodytes versus (chimpanzee). Papio anubis (olive baboon). Pongo Pygmaeus (orangutan). Macaca nemestrina (pig-tailed macaque) 5 to 75 mg/kg: Presbytis entellus (entellus langur) 3 to 5 mg/kg: Gorilla gorilla gorilla (gorilla) 7 to 10 mg/kg: Aotus trivirgatus (night monkey) 10 to 12 mg/kg: and Macaca tascicularis (crab-eating macaque). Macaca radiate (bonnet macaque). and Saimiri sciureus (squirrel monkey) 12 to 15 mg/kg. A single intramuscular injection produces restraint suitable for TB testing: radiography, physical examination, or blood collection.

HOW SUPPLIED Vetalar is supplied as the hydrochloride in concentrations equivalent to **ketamine** base.

N 0071-5584-10 Each 10 ml vial contains 100 mg/ml. Supplied in individual multi-dose vials (Steri Vials) and in cartons of 10.

CLINICAL STUDIES Vetalar has been clinically studied in subhuman primates in addition to those species listed under Dosage and Administration. Dosages for restraint in these additional species, based on limited clinical data, are Cercopithecus aethiops (grivet). Papio papio (guinea baboon) 10 to 12 mg/kg. Erythrocebus paths patas (patas monkey) 3 to 5 mg/kg: Hylobates lar (white-handed gibbon) 5 to 10 mg/kg: Lemur catta (ringtailed lemur) 7.5 to 10 mg/kg: Macaca fuscata (Japanese macaque) 5 mg/kg: Macaca speciosa (stumptailed macaque) and Miopithecus talapoin (mangrove monkey) 5 to 75 mg/kg: and Symphalangus syndactylus (siamangs) 5 to 7 mg/kg. ---------- Taxonomy from "A Handbook of Living Primates" by Napier and Napier Academic Press. New York, NY.

Occupational Safety & Health Administration
200 Constitution Avenue, NW
Washington, DC 20210

From World Federation of Societies of Anaesthesiologists
Comments on review of WHO / EML Anaesthetic drugs and muscle relaxants
Dr Michael Dobson

Comments on ISDB single medicines review – Anaesthetic Ether

Introduction.
It is not true to say that halothane is more stable and safer to use than ether. Anaesthetic halothane is in fact subject to spontaneous oxidation and this process has to be restrained by the addition of preservatives which in turn introduce a technical problem since the **preservative** accumulates inside anaesthetic vaporisers causing them to need more frequent repairs and service than those used with other volatile agents. In physiological terms there is absolutely no question that ether is the safer agent since it increases cardiac output and stimulates respiration whereas halothane is a severe depressant of both. This is of great importance in those hospitals (e.g. 75% of the district hospitals in Tanzania) where there is no regular oxygen supply.

Paragraph 4 line 2 should read: the concentration is three to five percent omitting the words "in air" which has no bearing on the anaesthetic concentration required.

Paragraph 5 – ether convulsions were last reported in textbooks published in the 1940s and 50s and WFSA does not believe that they are a significant clinical problem worthy of such a warning. Almost certainly many of these cases came from excessive doses of atropine, which prevents sweating and allowed children to develop febrile convulsions in a hot climate.

The following sentence "ether causes vasodilatation that may lead to a substantial fall in blood pressure and reduce renal blood flow" is simply not true. Ether causes less vasodilatation than any other volatile agent, it increases the cardiac output and the reduction in blood pressure is less than any other volatile agent. We are also very suspicious about the claim that ether can prolong prothrombin time and would

wish to see the evidence for this since we are not aware of any.

Page 2, paragraph 4 correctly states that ether stimulates respiration and circulation – this is in contradiction of the incorrect statement on page 1 on which I have already commented. *The paragraph on page 2 correctly points out that in a fit patient ether is the only volatile agent which is compatible with air as carrier gas and this is of huge significance in those hospitals where the supple of medical oxygen is not guaranteed. WFSA would say that all other volatile agents (other than ether) require the addition of supplementary oxygen.*

Paragraph 6 recommendation: we endorse the statement that ether should continue to be listed because of its low cost and relative safety in inexperienced hands. However, a further recommendation is given in this paragraph which is more problematic. There is no doubt that halothane is a cheap and effective alternative which when oxygen is available may be substantially more convenient to use and can indeed be used with great safety by appropriately trained people. Its use, however, requires a specific and different vaporiser from that used for ether as do

the other agents mentioned. We are particularly concerned about the mention of sevoflurane which is so expensive in western hospitals that its use there is severely restricted on a cost basis. We are not aware of any property of sevoflurane which would justify its recommendation over and above other less expensive volatile agents such as halothane and isoflurane.

A further problem is that we have been unofficially informed that many manufacturers are seeking to discontinue the production of halothane mainly because in western countries its use has diminished with the rise of alternative agents, chiefly isoflurane. Isoflurane is generally much cheaper than sevoflurane and if another agent than halothane is mentioned then isoflurane is much more suitable.

We wish to urge WHO to take all steps possible to make sure that effective drugs which are widely used in the developing world and which cannot be simply substituted over night do not have their production cut off by manufacturers simply because the financial returns are low.

ISDB SECTION REVIEW – DRUGS USED IN ANAESTHESIA

Sections 1.1 to 1.4

Page 1: Summary of recommendations

Thiopentone – recommendations fully supported

Ketamine – recommendations fully supported but please note that the **ketamine** formulation you plan to retain contains **preservative** and is not suitable for some of the unorthodox techniques which appear to be recommended on page 11.

Anaesthetic ether – we support the recommendation to retain

Halothane – we support the recommendation to retain

Nitrous Oxide – although widely used in industrialised countries nitrous oxide is expensive, and is not widely available in the majority of developing countries. Its use introduces risks of hypoxia when intensive gas monitoring is not available and we therefore do not regard it as an essential drug.

Oxygen – we support the recommendation to retain with an *added recommendation to give more information about the use of oxygen concentrators.*

Bupivicaine – we support the recommendation to retain
Lidocaine – we support the recommendation to retain
Ephedrine – we support the recommendation to retain
Epinephrine – support the recommendation to retain
Atropine sulphate – support the recommendation to retain
Diazepam – support the recommendation to retain

Promethazine – our opinion is that this drug is hardly used now for premedication and *cannot be regarded as essential*
Alcuronium – although this drug is included as a representative we have doubts as to whether it is actually manufactured or used anywhere in the world and strongly suggest that the representative drug for this class should in future be vecuronium.

Vecuronium bromide – we support the recommendation to retain
Atracurium – this product is heat labile and therefore its efficacy is in doubt unless there is a guaranteed cold chain. This should be made clear if the drug is mentioned in the list.
Suxamethonium chloride – liquid for injection is sensitive to heat and requires a cold chain. At the moment we are unable to identify a source of powered drug which is preferable for all tropical areas. Could WHO please investigate and give a source if possible.
Neostigmine – we support the recommendation to retain.

INDIVIDUAL PRODUCT REVIEWS

Thiopentone sodium.
Paragraph 6 - dosage
The dosage given in milligrams is insufficient for most adults (100:150 milligrams), 4-5 milligrams per kilogram (also given in this paragraph is satisfactory). The review seems to give a great deal of attention to accidental intra arterial injection which has not clinically been a problem for the last 40 years. It is sufficient to give a general recommendation that the drug should be given by indwelling cannula into a vein of the hand, wrist or forearm.

Page 6 – Contraindications
The first three of these are absolute, the rest are relative and some of the latter are not helpful eg obstetrics. Excessive dosages of all drugs are in all circumstances harmful and obstetrics does not need to be singled out for mention in this respect.

Page 7 – Evidence of value
It is *incorrect and dangerous* advice that propofol induction uses more stable haemodynamics dynamics than thiopentone. In fact the reverse is true and this incorrect statement is repeated twice on the page.

Page 11 – **Ketamine**
Epidural administration of **ketamine** is an unorthodox technique and if it is used the **ketamine** formulation must be **preservative** free. However, the preparation listed in the WHO formulary is intended for multidose intramuscular use and does contain **preservative**. It should therefore not be used in this way.

Page 12 – paragraph 6
The authors seem to be confusing cloning with coning!

Page 13 – paragraph 2
The use of **ketamine** and lidocaine spray is an unorthodox technique which is inadequately described here and not recommended. Such advice has no place in a formulary.

Page 13 – paragraph 6
The use of **ketamine** for intravenous regional anaesthesia is quirky, irrelevant and dangerous.
Final paragraph – the role of **ketamine** as an analgesic is well established rather than "being explored".

Page 19 – Halothane – contraindications
Halothane is not contraindicated in early pregnancy. It is true that the use of halothane results in a moderate increase in postpartum bleeding and in this respect it is not different from any other volatile anaesthetic agent.

Page 23 – Nitrous Oxide – paragraph 3
Entonox is expensive and has very limited geographical availability. It is therefore not worth mentioning in a document for world wide circulation.

Page 24 – contraindications
Any pneumothorax not just a tension pneumothorax is an absolute contraindication to the use of nitrous oxide. Decompression sickness is not a contraindication at all.

Page 25 – recommendation
Although a number of disadvantages of nitrous oxide are listed. The main ones are not listed, these are:

- the use of nitrous oxide immediately introduces the potential for giving a patient a hypoxic or anoxic gas mixture to breathe with fatal results.
- It is a requirement of the international and many national standards that nitrous oxide can only be given when sophisticated monitoring of inhaled gas concentrations can be guaranteed.
- This adds further to the cost of using nitrous oxide which is already an expensive drug. In most developing countries it costs around six times more per litre than in the industrialised west.

Nitrous oxide has only ever been used widely in western industrialised countries and its use in these countries is slowly diminishing. WFSA does not regard it as an essential drug.

Page 27 –oxygen – paragraph 4
It is unfortunately not true that oxygen is relatively inexpensive. Many large teaching hospitals in developing countries have had their oxygen supplies cut off because

they have been unable to pay the bills. For this reason it is important that people learn how to use oxygen effectively and economically and also know about oxygen concentrators which can produce oxygen for about 30% of the price for supplying it in cylinders. Information about this is available within WHO from Essential Health Technology.

Page 28 –line 2
Should read *concentration* control not *flow* control (these are not the same)

Paragraph 2
Many hospitals use cold water humidifiers (bubbling the oxygen through a jar of cold water). These are not only ineffective as humidifiers but introduce a substantial

infection risk as the water rapidly becomes colonised with bacteria. In the absence of heated blower humidifiers we recommend that humidifiers are not used especially with devices such as nasal prongs or venturi masks which allow the patient to use their own natural nasal humidifier.

Paragraph 4
Acute C02 retention caused by oxygen therapy is in fact extremely rare, as is pulmonary toxicity, except in intubated ventilated patients with severe multi system disease. The mention of cerebral toxicity from hyperbaric oxygen is largely irrelevant here.
Mention should be made of the increasing use of pulse oximeters which are available in many countries of the world to ensure that enough oxygen is given and no more. Raising oxygen saturations to 90 to 95% is always a safe thing to do and a pulse oximeter can indicate when the correct level has been reached.

Page 28 – final paragraph
Acute respiratory infection should be listed instead of pneumonia.

Page 31 – Bupivicaine
Paragraph 2 is incorrect: *levobupivacaine* is in fact bupivacaine (its L optical isomer), while ropivacaine is a separate and different drug not separated into optical isomers. Both these drugs are slightly less cardiotoxic than the standard racemic mixture of bupivacaine but both are significantly more expensive and are not widely available.

Paragraph 6

We wish to state categorically that bupivacaine must never under any circumstances be used for intravenous regional anaesthesia. There have been many case reports of this producing ventricular fibrillation which is not amenable to defibrillation.

Page 32

The contraindications listed are somewhat confusing because some of them are contraindications to the use of bupivacaine while others are general contraindications to the use of regional anaesthesia with any local anaesthetic agent.

Page 35 - Lidocaine

Page 36

It should be made clear that lidocaine is completely ineffective as a surface anaesthetic on intact skin although it works well on mucous membranes. Lidocaine toxicity is in general less serious than that of bupivacaine because lidocaine is relatively more toxic to the CNS than to the cardiovascular system with bupivacaine the reverse is true, and clinical experience confirms that a fit caused by lidocaine is unlikely to be fatal whereas ventricular fibrillation caused by bupivacaine is very likely to be fatal.

Page 39 – Ephedrine

Dosage – a maximum cumulative dose of 60mg for an adult is certainly permissible. The use of intramuscular ephedrine is not recommended.

Page 40

If a patient needs ephedrine he or she should not be denied it because they are athletes or sports persons. This contraindication has been put in because some sources mistakenly regard ephedrine as a performance enhancing drug, which in fact it is not. Any person requiring ephedrine as a medical treatment should receive it; subsequently they may need to be advised not to compete in the 100 metres for a while!

Paragraph 6

The use of *ephedrine is not associated at all with nausea and vomiting*. Maternal

hypotension routinely causes nausea and vomiting. Ephedrine is the treatment and once the blood pressure has been restored the symptoms of nausea and vomiting invariably disappear.

Page 43 – Epinephrine
There should be a note that the inset and off set of the effect of epinephrine are both very rapid. If given for support for cardiovascular system it must therefore be given as a continuous infusion.

Page 49 Atropine
The routine use of atropine premedication is unnecessary except when it precedes inhalational induction with ether (rare in practice) or intramuscular **ketamine** (and in fact in the latter case it can be mixed with **ketamine** and given by the same injection.

Page 50 – Contraindications
Gastro-oesophageal reflux, glaucoma, and prostatic enlargement are not contraindications to the anaesthetic use of a single dose of atropine.

Page 51, paragraph 7 (commencing "Intramuscular meperidine")
This is irrelevant to a description of atropine and the paragraph should be omitted.

Page 55 – Diazepam – Adverse reactions
Clear statement is needed that intravenous diazepam can cause airway obstruction and hypoxia in exactly the same way as any other intravenous anaesthetic.

Page 66 – Promethezine
It is WFSA's believe that this drug is only very rarely used in premedication and is not essential.

Page 67 – Alcuronium
We do not believe this drug is currently in manufacture. It offers no advantages over vecuronium and we agree with the recommendation that it be deleted and vecuronium inserted as a representative neuromuscular blocker.

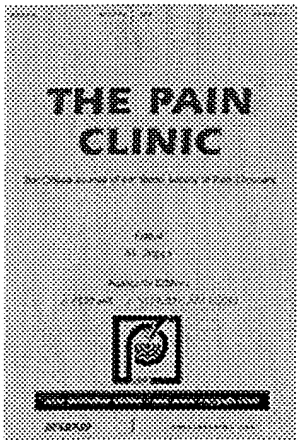
Page 71 – Vecuronium
Paragraph 2
Respiratory paralysis should be expected after giving *any* muscle relaxant and not regarded as an adverse event.

Paragraph 3
There are no special risks of giving vecuronium in pregnancy.

Page 74 – Atracurium
This is a heat-labile drug. We do not recommend its inclusion unless there is a clear statement that a continuous cold chain from manufacturer to patient must be maintained.

Page 77 - Suxamethonium
Paragraph 4
The powder to be reconstituted is very desirable since unlike the liquid formulation it is not heat-labile, but in our experience the powder is very difficult if not impossible to obtain. If WHO is able to recommend a source for this to WFSA we would be most grateful and we also feel that a specific statement about heat-lability of the liquid formulation should be in the model list.

Dated 3 January 2005 (received 12 January 2005)



Repeated epidural injections of ketamine with preservative benzethonium chloride produce evidence for neurotoxicity in rabbits

Journal The Pain Clinic
Publisher Brill Academic Publishers
ISSN 0169-1112 (Print) 1568-5691 (Online)
Subject Behavioral Science and Humanities, Social Sciences and Law
Issue Volume 15, Number 3 / September, 2003
DOI 10.1163/156856903767650835
Pages 299-307
Online Date Friday, November 12, 2004

E. Alp Yentur, Idil Tekin Mirzai, Hasan Mirzai, Utku Ates, Meral Baka and Mine Yurtseven

Abstract *Background and objectives*: In this study, we investigated whether repeated doses of 1% ketamine with preservative benzethonium chloride, administered into the epidural space of the rabbit, caused direct neurotoxicity.___TAGSTART___BR___TAGEND___ *Methods*: Twelve rabbits were randomly assigned to two groups (ketamine and control). After the animals were anesthetized, lumbar epidural catheters were placed for repeated epidural drug delivery. The ketamine group received 1% ketamine with preservative benzethonium chloride (0.5 ml) and the control group received isotonic saline (0.5 ml) once a day for 14 consecutive days. The day after the last injection, the animals were reanaesthetized, the left and right ventricles were cannulated and perfused with 2% glutaraldehyde, 1% formaldehyde mixture, in 0.1 mol/l phosphate buffer. Then, laminectomy was performed. A five centimetre segment of the spinal cord was removed and examined by light and electron microscopy to observe possible histological changes. Microscopic examinations were performed by coding each animal by a neuro-histologist who was blinded as to the source of each specimen.___TAGSTART___BR___TAGEND___ *Results*: Ketamine-treated rabbits showed

significant histological changes at light and electron microscopy findings compared with the control group ($p >$ 0.05).___TAGSTART___BR___TAGEND___ *Conclusions*: These changes suggested a neurotoxic effect of ketamine with preservative benzethonium chloride following chronic epidural administration.

Epidural catheter - ketamine - neurotoxicity.

references

1. Schmida RL, Sandlera AN, Katza J, Review Article: Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes, *Pain* **82**, 111–25 (1999).

2. Brock-Utne JG, Mankowitz E, Kallichurum S, et al., Effects of intrathecal saline and ketamine with and without preservative on the spinal nerve roots of monkeys, *S Afr Med J* **61**, 360–1 (1982).

3. Malinovsky JM, Cozian A, Lepage JY, et al., Ketamine and midazolam neurotoxicity in the rabbit, *Anesthesiology* **75**, 91–7 (1991).

4. Malinovsky JM, Lepage JY, Cozian A, et al., Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* **78**, 109–15 (1993).

5. Borgbjerg FM, Svensson BA, Frigast C, et al., Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabbit: a light and electron microscopic examination, *Anesth Analg* **79**, 105–11 (1994).

6. Brock-Utne JG, Kallichurum S, Mankowitz E, et al., Intrathecal ketamine with preservative— histological effects on spinal nerve roots of baboons, *S Afr Med J* **61**, 440–1 (1982).

7. Erdine S, Yucel A, Ozyalcin S, et al.,

Neurotoxicity of midazolamin the rabbit, *Pain* **80**, 419–23 (1999).

8. Yaksh TL, Epidural ketamine: a useful, mechanistically novel adjuvant for epidural morphine? *Reg Anesth* **21**, 508–13 (1996).

9. Amiot JF, Palacci JH, Vedrenne C, et al., Toxicité médullaire de I''acétyl salicylate de lysine et du chlorhydrate de kétamine administrés par voie intrathécale chez le rat, *Ann Fr Anesth Reanim* **5**, 462 (1986).

10. Errando C, Spinal toxicity of drugs: some specifications about ketamine, *Anesth Analg* **90**, 227 (2000).

11. Errando CL, Sifre C, Moliner S, et al., Subarachnoid ketamine in swine–pathological findings after repeated doses: acute toxicity study, *Reg Anesth Pain Med* **24**, 146–52 (1999).

12. Bion JF, Intrathecal ketamine for war surgery: A preliminary study under field conditions, *Anaesthesia* **39**, 1023–8 (1984).

British Journal of Anaesthesia

BJA Advance Access originally published online on January 22, 2004

British Journal of Anaesthesia, 2004, Vol. 92, No. 3 **344-347**

Clinical Investigations

Double-blind randomized controlled trial of caudal *versus* intravenous S(+)-ketamine for supplementation of caudal analgesia in children

S. J. Martindale, P. Dix and P. A. Stoddart*

Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol BS2 8BJ, UK

**Corresponding author. Email: Peter.Stoddart@ubht.swest.nhs.uk*

Accepted for publication: July 29, 2003

Abstract

Background. The postoperative analgesic efficacy of S(+)-ketamine after caudal or i.v. administration following sub-umbilical surgery in children was studied to investigate its principal site of analgesic action.

Methods. Sixty children undergoing caudal block during general anaesthesia for hernia repair or orchidopexy were prospectively randomized to one of three groups: the bupivicaine group received plain

bupivacaine 0.25% 1 ml kg^{-1}; the caudal ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} with S (+)-ketamine 0.5 mg kg^{-1}; the i.v. ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} plus S(+)-ketamine 0.5 mg kg^{-1} i.v.. Postoperative measurements included analgesic requirements and modified objective pain score for the first 24 h.

Results. The median time to first analgesia was significantly longer in the caudal ketamine group (10 h) than in the i.v. ketamine (4.63 h) or bupivacaine (4.75 h) groups (P=0.01). Significantly fewer doses of analgesia were required over the first postoperative 24 h by subjects in the caudal ketamine group (median 1) compared with the i.v. ketamine (median 2) or bupivacaine (median 2.5) groups (P<0.05). There was no difference between the groups in the incidence of postoperative nausea and vomiting or psychomotor reactions.

Conclusions. We have demonstrated that the addition of caudal S(+)-ketamine to bupivacaine prolongs the duration of postoperative analgesia. However, the same dose of i.v. S(+)-ketamine combined with a plain bupivacaine caudal provides no better analgesia than caudal bupivacaine alone, indicating that the principal analgesic effect of caudal S(+)-ketamine results from a local neuroaxial rather than a systemic effect.

Br J Anaesth 2004; **92**: 344–7

Keywords: anaesthesia, paediatric; anaesthetic techniques, regional, caudal; anaesthetics i.v., ketamine; anaesthetics local, bupivacaine

Introduction

Caudal analgesia with bupivacaine is commonly used in paediatric surgery where the operative site is sub-umbilical.[1] However, a single injection has a short duration of action and more than 60% of children undergoing orchidopexy with this technique require further analgesia during the postoperative period.[2]

Caudal ketamine has been shown to prolong the duration of postoperative analgesia in children undergoing orchidopexy[3] and inguinal herniotomy.[4] Despite numerous published reports of the safe use of racemic ketamine, this substance has not been adopted widely, because of the potential neurotoxicity of preservative agents contained in commercially available preparations.[5] However, S(+)-ketamine, one of two enantiomers of racemic ketamine, has twice the analgesic potency of the racemate[6] and is available as a preservative-free drug which has potential for epidural administration.

At anaesthetic doses, systemic administration of ketamine has been limited by undesirable emergence phenomenon, psychomimetic reactions and cardiovascular stimulating properties. However, sub-anaesthetic i.v. doses of ketamine can provide an adjunct to systemic opioid analgesia with few side-effects,[7,8] though we have been unable to demonstrate this in children following appendicectomy.[9]

Although there has been one study comparing caudal with i.m. S(+)-ketamine,[10] we are unaware of any studies comparing caudal with i.v. S(+)-ketamine. We proposed to investigate the postoperative analgesic efficacy of low-dose S(+)-ketamine administered either caudally or i.v. to supplement a plain bupivacaine caudal during sub-umbilical surgery in children in order to investigate the site of analgesic action.

Patients and methods

Top
Abstract
Introduction
Patients and methods
Results
Discussion
References

The study was approved by the local ethics committee and after obtaining written and informed parental consent, we recruited 60 children aged 3 months to 6 yr in a prospective, randomized, double-blind study. Any child for whom there was a contraindication to caudal block was not studied. Children undergoing day-case hernia repair or orchidopexy were allocated randomly, using sealed envelopes, to one of three groups for caudal block: the bupivicaine group received plain bupivacaine 0.25% 1 ml kg^{-1}; the caudal ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} with S(+)-ketamine 0.5 mg kg^{-1}; the i.v. ketamine group received caudal plain bupivacaine 0.25% 1 ml kg^{-1} plus (+)-ketamine 0.5 mg kg^{-1} i.v.. Drugs were prepared by a person not otherwise involved in the study.

All children received paracetamol 20 mg kg^{-1} as premedication, and Ametop cream to the dorsum of the hand at least 20 min before surgery. Induction of anaesthesia was with either propofol 3–4 mg kg^{-1} or inhalational with sevoflurane 8%, followed by placement of a laryngeal mask airway. Anaesthesia was maintained with isoflurane 1.5–2.0% and nitrous oxide 70% in oxygen.

A caudal block was then established under aseptic conditions with the child in the left lateral position. Full monitoring was used throughout the anaesthetic period. Each child was given diclofenac 1 mg kg^{-1} *per rectum* intraoperatively. No opioids or other analgesics were administered intraoperatively. In the recovery ward, normal observations were taken every 15 min until discharge to the ward. The duration of motor blockade was assessed by determining when patients began to move their legs. The time of first micturition was noted. Assessments of the level of sedation were made at 1, 2 and 4 h, using an objective score based on eye opening (eyes open spontaneously=0; eyes open in response to verbal stimulation=1; eyes open in response to physical stimulation=2).

The efficacy of postoperative analgesia was documented using the modified objective pain score (OPS) for the assessment of postoperative pain and by duration of analgesia after caudal block. The OPS is an observational pain scoring system which has been validated for use by parents.[11] The score uses five criteria: crying, agitation, movement, posture and localization of pain. Each criterion scores from 0 to 2 to give a total score of 0–10. Duration of analgesia was defined as the time between caudal injection of the drug and first administration of postoperative analgesia. If analgesia was not required within the 24 h observation period, duration of analgesia was counted as 24 h.

Analgesia was given to children when their OPS reached 4 or more and consisted of paracetamol 15 mg kg^{-1} by mouth every 4 h as required. All assessments in the hospital were performed by observers who were unaware of the mixture used to provide caudal epidural blockade.

After discharge 4–6 h after surgery, parents were asked to assess the child regularly and give analgesia if the OPS reached 4 or more. Parents were contacted by telephone 24 h after surgery to determine the analgesic requirements at home, the timing of micturition and any evidence of nightmares, hallucinations or odd behaviour. The total requirement for postoperative analgesia in the 24 h period was noted.

Power analysis for duration of analgesia was calculated using data from previous studies. Assuming a 100% difference exists between the ketamine groups and the bupivacaine group, 20 patients in each group allows a greater than 95% chance of detecting a difference in the time to first analgesia at the usual level of significance (α=0.05). Data are presented as median and interquartile range because of the skewed distribution of the data; statistical analysis was

completed using the Kruskal–Wallis test for non-parametric data.

Results

Top
Abstract
Introduction
Patients and methods
Results
Discussion
References

One subject in the caudal ketamine group was excluded from analysis because he did not undergo the scheduled surgery. Patient characteristics, type and duration of surgery were similar in the three groups with the exception of age in the i.v. ketamine group (Table 1). Despite the difference in age in the i.v. ketamine group, which arose by chance, there was no difference in median number of analgesic doses between the children aged 3–18 months (2 (interquartile range 1–3)), 18–36 months (2 (1–3)) and 36–71 months (1 (1–3.5)), irrespective of the group to which they were randomized (P=0.89). Additionally, the apparent difference between the groups in the type of operation was not significant (P=0.35) and furthermore did not affect analgesic requirements. Children who underwent orchidopexy (n=34) showed a median time to first analgesia of 5.63 (3.56–11.06) h and the number of analgesic doses was 2 (1–3.25) compared with hernia repair (n=25) with a median time to first analgesia of 5.0 (4.1–10) h and number of analgesics of 2 (1–3) (P=0.69 and 0.88, respectively), irrespective of which treatment group they were in. Thus valid comparisons could be made between all three groups.

View this table: [in this window] [in a new window]

Table 1 Patient characteristics. Results are median (interquartile range) or numbers

The median duration of action of the technique employed, as indicated by the time to first analgesia, was significantly longer in the caudal ketamine group (10 h (5.2–19)) than in the i.v. ketamine group (4.63 h (3–7.44)) or bupivacaine group (4.75 h (3.2–7.05)) (P=0.01) and there were no significant differences between the i.v. ketamine and bupivacaine groups. Significantly fewer doses of analgesia were required over the first 24 h after surgery by subjects in the caudal ketamine group (1 (1–2)) compared with the i.v. ketamine group (2 (1–3)) or bupivacaine group (2.5 (1.25–4)) (P=0.01) and once again there was no significant difference between the latter two groups. Four patients in the caudal ketamine group did not require any postoperative analgesia.

The times to first micturition and spontaneous leg movements were similar in the three groups (Table 2).

View this table: [in this window] [in a new window]

Table 2 Time to micturition and spontaneous leg movements. Data are median (interquartile range)

The OPS at 1, 2, 4 and 24 h after surgery are shown in Table 3. There were no significant differences between the groups at any time. There was no difference between the groups in sedation scores (median 2 in all three groups at 1, 2, 4 and 24 h) nor in the incidence of early or late vomiting (median 0 in all three groups at 1, 2, 4 and 24 h), with only seven children requiring anti-emetics. There were two children in whom vacant stares were reported by the parents before bedtime. These were short lived, having completely resolved by the next morning, and neither the parents nor the children appeared distressed by them. One child had received i.v. ketamine and the other had not received ketamine. These children had both met the strict criteria for discharge from the day surgery unit.

View this table: **Table 3** Objective pain scores after surgery. Data are median (interquartile range)
[in this window]
[in a new window]

Discussion

Top
Abstract
Introduction
Patients and methods
Results
Discussion
References

Our study was designed to compare whether the addition of S(+)-ketamine to bupivacaine, when administered caudally, would prolong the duration of postoperative analgesia more than i.v. S(+)-ketamine combined with caudal bupivacaine in children undergoing orchidopexy or herniorrhaphy. The results indicate that caudal S(+)-ketamine and bupivacaine combined, prolonged postoperative analgesia by 6 h and significantly reduced the need for subsequent postoperative analgesia by more than 50% compared with caudal bupivacaine alone or i.v. S(+)-ketamine plus caudal bupivacaine.

There was no difference in postoperative sedation or in OPS between the groups at any of the time intervals studied, which is not unexpected since supplemental analgesia was given to any child whose OPS reached 4 or more. Nausea and vomiting was not a major problem in any of the groups. While motor block did occur in all groups, it was not a major problem and was shown to be no worse in the ketamine groups than in the bupivacaine group. There was no significant difference in the time to first micturition between the groups, although one child in the caudal ketamine group did have a prolonged time of 17 h.

These findings support those of other workers confirming that ketamine supplementation of bupivacaine prolongs the duration of caudal epidural blockade.[12] However, our results also demonstrate that caudal S(+)-ketamine provides more effective analgesia than i.v. S(+)-ketamine, which suggests that the analgesic effect of the caudally administered drug is caused by a direct effect on the spinal cord.

Ketamine, a derivative of phencyclidine, works at a number of different target sites which could explain this analgesic effect in the spinal cord. It is an antagonist at *N*-methyl-D-aspartate (NMDA) receptors, with a stereoselectivity in favour of S(+)-ketamine.[13] NMDA receptors are found throughout the central nervous system, including the lumbar spinal cord, and play an important role in nociceptive processing.[14] Analgesic effects may also result from agonist activity at mu-opioid receptors[15] and interaction with voltage-sensitive sodium channels.[16] Furthermore, the binding site of ketamine at mu-opioid receptors appears to be stereoselective for the S(+)-enantiomer.[17]

The use of caudal ketamine may elicit concern about potential neurotoxicity. No major sequelae have been reported after the use of caudal ketamine 1% in human studies. Animal studies have demonstrated the safety of intrathecal ketamine 1% after a single dose[18–20] and after multiple doses.[21] One study has claimed to show a definite neurotoxic effect of ketamine 1%[22] but those same workers subsequently demonstrated that it was the preservative chlorbutanol administered intrathecally that caused neurotoxicity whereas ketamine without preservative did not.[20] As far as ketamine is concerned, a review on the neurotoxicity of intrathecally administered drugs concluded that "taken together, the rat, rabbit, and primate studies with intrathecal ketamine support its safety if used without a preservative whereas the commercially available preparation of ketamine contains an untested preservative (benzethonium chloride) and cannot be recommended for intrathecal use in humans". [23]

Acknowledgements

We would like to thank the nurses of the day case unit at Bristol Children's Hospital for their assistance with the data collection, our anaesthetic and surgical colleagues at the hospital for allowing us to recruit their patients and Dr A. Black for his assistance with the statistical analysis.

References

- Top
- Abstract
- Introduction
- Patients and methods
- Results
- Discussion
- References

1 Melman E, Penuelas JA, Marrufo J. Regional anesthesia in children. *Anesth Analg* 1975; **54**: 387–90[Abstract]

2 Wolf AR, Hughes D, Wade A, Mather SJ, Prys-Roberts C. Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine-morphine mixture. *Br J Anaesth* 1990; **64**: 430–5[Abstract]

3 Findlow D, Aldridge LM, Doyle E. Comparison of caudal block using bupivacaine and ketamine with ilioinguinal nerve block for orchidopexy in children. *Anaesthesia* 1997; **52**: 1110–13[ISI][Medline]

4 Naguib M, Sharif AM, Seraj M, el Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: comparison with caudal bupivacaine. *Br J Anaesth* 1991; **67**: 559–64[Abstract]

5 Gebhardt B. Pharmacology and clinical results with peridural and intrathecal administration of ketamine. *Anaesthesist* 1994; **43**(Suppl 2): S34–40[ISI][Medline]

6 Adams HA, Werner C. From the racemate to the eutomer: (S)-ketamine. Renaissance of a substance? *Anaesthesist* 1997; **46**: 1026–42[CrossRef][ISI][Medline]

7 Owen H, Reekie RM, Clements JA, Watson R, Nimmo WS. Analgesia from morphine and ketamine. A comparison of infusions of morphine and ketamine for postoperative analgesia. *Anaesthesia* 1987; **42**: 1051–6[ISI][Medline]

8 Jahangir SM, Islam F, Aziz L. Ketamine infusion for postoperative analgesia in asthmatics: a comparison with intermittent meperidine. *Anesth Analg* 1993; **76**: 45–9[Abstract]

9 Dix P, Martindale S, Stoddart PA. Double-blind randomized placebo-controlled trial of the effect of ketamine on postoperative morphine consumption in children following appendicectomy. *Paediatr Anaesth* 2003; **13**: 422–6 [CrossRef][ISI][Medline]

10 Koinig H, Marhofer P, Krenn CG, *et al.* Analgesic effects of caudal and intramuscular S(+)-ketamine in children. *Anesthesiology* 2000; **93**: 976–80[CrossRef][ISI][Medline]

11 Wilson GA, Doyle E. Validation of three paediatric pain scores for use by parents. *Anaesthesia* 1996; **51**: 1005–7 [ISI][Medline]

12 Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *Br J Anaesth* 1995; **75**: 698–701 [Abstract/Free Full Text]

13 Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. *Eur J Pharmacol* 1992; **213**: 155–8[CrossRef][ISI][Medline]

14 Coggeshall RE, Carlton SM. Receptor localization in the mammalian dorsal horn and primary afferent neurons. *Brain Res Rev* 1997; **24**: 28–66[ISI][Medline]

15 Smith DJ, Bouchal RL, deSanctis CA, *et al.* Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* 1987; **26**: 1253–60[CrossRef][ISI][Medline]

16 Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996; **77**: 441–4[Free Full Text]

17 Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG. Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. *Anesthesiology* 1999; **90**: 174–82[CrossRef][ISI][Medline]

18 Brock-Utne JG, Mankowitz E, Kallichurum S, Downing JW. Effects of intrathecal saline and ketamine with and without preservative on the spinal nerve roots of monkeys. *S Afr Med J* 1982; **61**: 360–1[ISI][Medline]

19 Brock-Utne JG, Kallichurum S, Mankowitz E, Maharaj RJ, Downing JW. Intrathecal ketamine with preservative – histological effects on spinal nerve roots of baboons. *S Afr Med J* 1982; **61**: 440–1[ISI][Medline]

20 Malinovsky JM, Lepage JY, Cozian A, Mussini JM, Pinaudt M, Souron R. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* 1993; **78**: 109–15[ISI][Medline]

21 Borgbjerg FM, Svensson BA, Frigast C, Gordh T, Jr. Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabbit: a light and electron microscopic examination. *Anesth Analg* 1994; **79**: 105–11 [Abstract]

22 Malinovsky JM, Cozian A, Lepage JY, Mussini JM, Pinaud M, Souron R. Ketamine and midazolam neurotoxicity in the rabbit. *Anesthesiology* 1991; **75**: 91–7[ISI][Medline]

23 Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). *Anesth Analg* 1999; **88**: 797–809[Free Full Text]

This article has been cited by other articles:

- **Abstract** FREE
- **Full Text (PDF)**
- **All Versions of this Article:**
  92/3/344 *most recent*
  aeh076v1
- **E-Letters: Submit a response to the article**
- **Alert me when this article is cited**
- **Alert me when E-letters are posted**
- **Alert me if a correction is posted**

Services

- **Email this article to a friend**
- **Similar articles in this journal**
- Similar articles in ISI Web of Science
- **Similar articles in PubMed**
- **Alert me to new issues of the journal**
- **Add to My Personal Archive**
- **Download to citation manager**
- **Search for citing articles in:**
  ISI Web of Science (5)
- **Disclaimer**
- **Request Permissions**

Google Scholar

- **Articles by Martindale, S. J.**
- **Articles by Stoddart, P. A.**

PubMed

- **PubMed Citation**
- **Articles by Martindale, S. J.**
- **Articles by Stoddart, P. A.**

Online ISSN 1471-6771 - Print ISSN 0007-0912

- Site Map
- Privacy Policy
- Frequently Asked Questions

Other Oxford University Press sites: Oxford University Press GO

About Entrez
Text Version
Entrez PubMed
Overview
Help | FAQ
Tutorials
New/Noteworthy
E-Utilities
PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI
Related Resources
Order Documents
NLM Mobile
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Note: Performing your original search, ***ketamine preservative***, in PubMed will retrieve 27 citations.

1: Anesthesiology. 1997 Jun;86(6):1326-33. Related Articles, Links

Synergistic inhibition of muscarinic signaling by ketamine stereoisomers and the preservative benzethonium chloride.

Durieux ME, **Nietgen GW**.

University of Virginia Health Sciences Center, Charlottesville 22906-0010, USA. med2p@virginia.edu

BACKGROUND: Ketamine (Ketalar; Parke-Davis, Morris Plains, NJ) has been shown to inhibit muscarinic signaling with a median inhibitory concentration (IC50) of 5.7 microM. Whereas Ketalar is a racemic mixture, recent interest has focused on clinical use of the S (+) ketamine isomer, which is three times as potent an analgesic as the R(-) isomer yet seems to be associated with fewer psychoactive side effects. Therefore, the authors studied the effects of S(+) and R(-) ketamine and the preservative benzethonium chloride on muscarinic signaling. METHODS: Rat ml muscarinic acetylcholine receptors were expressed recombinantly in Xenopus laevis oocytes. Ca2(+)-activated Cl- currents in response to 10(-7) M acetyl-beta-methylcholine were determined by two-electrode voltage clamping in the presence of various concentrations of ketamine and benzethonium. Concentration-inhibition curves were constructed and used for algebraic and isobolographic analysis. RESULTS: The IC50. was 125 +/- 33 microM for S(+) ketamine, and 91 +/- 19 microM for R(-) ketamine. This difference was not statistically significant, indicating that muscarinic inhibition by ketamine is not stereoselective. The R(-)/S(+) mixture had an IC50 of 48 +/- 1 microM, and thus the stereoisomers interact synergistically. When appropriate concentrations of benzethonium were added, an IC50 of 15 +/- 2 microM resulted. CONCLUSIONS: The muscarinic inhibitory action of ketamine isomers is not stereoselective. Because S(+) ketamine is a significantly more potent analgesic, it should have less muscarinic inhibitory action than R(-) ketamine when used in clinically equivalent doses. A significant fraction of the muscarinic inhibitory action of Ketalar is due to the preservative benzethonium. If reconstituted with a different preservative, Ketalar might be a less potent muscarinic antagonist.

PMID: 9197302 [PubMed - indexed for MEDLINE]

Display Abstract Show 20 Sort by Send to

About Entrez
Text Version
Entrez PubMed
Overview
Help | FAQ
Tutorials
New/Noteworthy
E-Utilities
PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI
Related Resources
Order Documents
NLM Mobile
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Note: Performing your original search, ***ketamine preservative***, in PubMed will retrieve *27* citations.

Display Abstract Show 20 Sort by Send to
All: 1 Review: 0

1: Br J Pharmacol. 2001 Oct;134(4):871-9. Related Articles, Links

nature publishing group

Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant alpha7 and alpha4beta2 neuronal nicotinic acetylcholine receptors in Xenopus oocytes.

Coates KM, Flood P.

Department of Anesthesiology, Columbia University, 630 West 168th Street, New York, NY 10032, USA.

1. Ketamine is a dissociative anaesthetic that is formulated as Ketalar, which contains the preservative benzethonium chloride (BCl). We have studied the effects of pure racemic ketamine, the preservative BCl and the Ketalar mixture on human neuronal nicotinic acetylcholine receptors (nAChRs) composed of the alpha7 subunit or alpha4 and beta2 subunits expressed in Xenopus laevis oocytes. 2. Ketamine inhibited responses to 1 mM acetylcholine (ACh) in both the human alpha7 and alpha4beta2 nAChRs, with IC(50) values of 20 and 50 microM respectively. Inhibition of the alpha7 nAChRs occurred within a clinically relevant concentration range, while inhibition of the alpha4beta2 nAChR was observed only at higher concentrations. The Ketalar formulation inhibited nAChR function more effectively than was expected given its ketamine concentration. The surprising increased inhibitory potency of Ketalar compared with pure ketamine appeared to be due to the activity of BCl, which inhibited both alpha7 (IC(50) value of 122 nM) and alpha4beta2 (IC(50) value of 49 nM) nAChRs at concentrations present in the clinical formulation of Ketalar. 3. Ketamine is a noncompetitive inhibitor at both the alpha7 and alpha4beta2 nAChR. In contrast, BCl causes a parallel shift in the ACh dose-response curve at the alpha7 nAChR suggesting competitive inhibition. Ketamine causes both voltage-dependent and use-dependent inhibition, only in the alpha4beta2 nAChR. 4. Since alpha7 nAChRs are likely to be inhibited during clinical use of Ketalar, the actions of ketamine and BCl on this receptor subtype may play a role in the profound analgesia, amnesia, immobility and/or autonomic modulation produced by this anaesthetic.

PMID: 11606328 [PubMed - indexed for MEDLINE]

Display Abstract Show 20 Sort by Send to

British Journal of Anaesthesia

British Journal of Anaesthesia, 2004, Vol. 92, No. 1 **152**

Correspondence

Preservative-free ketamine

N. C. Huddy[1], K. Kiff[1], M. L. Thomas[2] and D. A. H. de Beer[2]

[1] Chelmsford, UK [2] London, UK

Editor—We were delighted to read the review article on 'Caudal additives in children—solutions or problems?'.[1] We have used preservative-free caudal ketamine for over 330 general surgical, urological and orthopaedic paediatric cases in Chelmsford since 1998, providing excellent, prolonged analgesia with no untoward effects.

In the authors' summary paragraph they conclude that 'a combination of ketamine 0.5 mg kg^{-1} and bupivacaine is even more effective [than clonidine 1 μg kg^{-1}], providing analgesia for up to 12 h'. These additives, they concluded, had superseded the use of caudal opioids and we wholeheartedly concur with these findings.

We were rather disappointed to then read: 'however, further study and the introduction of ketamine into mainstream clinical practice is limited by the difficulties in obtaining preservative-free ketamine and ongoing concerns about potential neurotoxicity'. They also state that 'the use of caudal additives for day-care anaesthesia is controversial and at present their routine use cannot be recommended'. We have obtained preservative-free ketamine 10 mg ml^{-1} (50 mg ampoules) on a named-patient basis since 1998 from Ketamin Curamed (Ketamine—Curamed Pharma GmbH, Postfach 41 02 29, D-76202 Karlsruhe, Germany).

The authors question the safety of epidural ketamine and quote a paper by Stotz.[2] This paper reported a case of a 72-yr-old woman who developed isolated lymphocytic vasculitis of the spinal cord and leptomeninges after a 7 day infusion of ketamine, clonidine, morphine and bupivacaine, although she showed no signs of neurological deficit. The ketamine used was the commercially available ketamine with benzethonium preservative. The patient had an intrathecal catheter *in situ* for 18 days, initially with morphine 0.12 mg ml^{-1} and bupivacaine 0.25% given at 2–2.5 ml h^{-1}. The dose was then increased to 3–3.5 ml h^{-1} and the morphine increased to 0.3 mg ml^{-1}. During this time, she developed signs of

meningitis. Stotz and colleagues concluded that 'the changes may be related to the preservative benzethonium chloride or the toxicity of the mixture itself'.[2] With regard to the use of caudal additives for day-care anaesthesia, we are at a loss to understand why the authors think that the addition of preservative-free ketamine to caudal bupivacaine should be controversial. Is it their worry of neurotoxicity or some other long-term side-effect that concerns them?

We feel that the addition of preservative-free ketamine to caudal bupivacaine is not only a good analgesic but should be the method of choice in this type of paediatric case.

N. C. Huddy

K. Kiff

Chelmsford, UK

Editor—We are pleased that Drs Huddy and Kiff enjoyed our recent review,[1] and we thank you for the opportunity to reply. With regard to the availability of preservative-free ketamine, we are glad to read the authors' ease in obtaining this, albeit on a named-patient basis. This necessarily cumbersome process represents a practical barrier to its more widespread acceptance. As was reported recently,[3] preservative-free ketamine is now available in this country and therefore no longer has to be imported directly from Germany. This, we trust, will increase the frequency with which it is used.

We were delighted to hear of yet more evidence, albeit anecdotal, of Drs Huddy and Kiffs' positive experiences with the drug as a caudal additive in children and would encourage them to formally report their data to add to the growing, yet still small, body of clinical evidence to support its use.

As regards neurotoxicity, Huddy and Kiff are quite correct in drawing attention to the equivocal aetiology of the only human case report of neurotoxicity associated with epidural ketamine. However, as stated in our review,[1] there is animal data of the vacuolation of posterior root ganglia attributable to ketamine, admittedly at high doses.

With regard to the use of caudal additives for day-case anaesthesia, we stand by our original statement and maintain that, at present, their routine use cannot be recommended. The reason for this relates to the potential problems that may arise after discharge as a result of prolonged sensory and motor block, in particular block of thermal sensibility.[4] While these problems might also occur with the use of plain bupivacaine, the use of additives such as clonidine and ketamine increases the risk.

We therefore feel it is worth exercising caution rather that advocating its widespread use while the body of clinical evidence tips ever more in favour of caudal ketamine.

M. L. Thomas

D. A. H. de Beer

London, UK

References

1 de Beer DAH, Thomas ML. Caudal additives in children—solutions or problems? *Br J Anaesth* 2003; **90**: 487–98

[Abstract/Free Full Text]

2 Stotz M, Oehen HP, Gerber H. Histological findings after long-term infusion of intrathecal ketamine for chronic pain: a case report. *J Pain Symptom Manage* 1999; **18**: 223–8[CrossRef][ISI][Medline]

3 Martindale M, Worsley M. Caudal additives in children—solutions or problems? *Br J Anaesth* 2003; **91**: 300–30 [Free Full Text]

4 Cooper R. Clonidine in paediatric anaesthesia. *Paed Anaesth* 2000; **10**: 223–4[CrossRef][Medline]

Online ISSN 1471-6771 - Print ISSN 0007-0912